Calcidiol level in patients with psoriasis treated with NB-UVB therapy

Stężenie kalcydiolu u chorych na łuszczycę leczonych fototerapią UVB 311

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Summary

Introduction. UVB 311nm phototherapy (NB-UVB) appears to influence the psoriasis significant factor’s genes expression by epidermal synthesis of vitamin D.

Aim. The aim of this research was to examine whether NB-UVB was able to induce 25(OH)D synthesis in relationship to its initial level and BMI, age, sex, nutrition and behavioral habits.

Material and methods. Serum 25(OH) D level was measured using RIA-method in 36 patients in T0 before the first dose of radiation, in T1-T3 during the treatment and in T4 and T5 accordingly in 1st and 5th week after the end of phototherapy. The parameters in controls (28 healthy adults) were measured in T0 and T4. Assessment included also: BMI, skin phototype, questionnaire (sun exposure, nutrition habits).

Results. Calcidiol level in T0 was higher in patients 33.21 ng/ml vs. 25.17 ng/ml in controls (p < 0.05). The tendency to lower calcidiol levels among older, women and in patients with a lower PASI index value wasn’t significant (p > 0.05). There was a statistically significant difference in the increase of calcidiol level in patients between T0 and T4 – higher in the group of level < 25 ng/ml. There was an increase of calcidiol level in patients in T4 – 50.16 ng/ml (p < 0.05) and a decrease in controls – 21.37 ng/ml. In T5 calcidiol level in patients was 51.18 ng/ml. 11-45% participants reported consumption of different dairy products. The consumption of fish was declared as at least once a month.

Conclusions. The initial level of 25(OH)D has an impact on its growth by NB-UVB. The dose of UVB 311 nm received during the irradiation masked seasonal variability of the calcidiol level. There was no effect of BMI or PASI index values, age or gender on the calcidiol level. Nutrition and behavioral habits have an impact on the calcidiol level.

Key words: psoriasis, NB-UVB phototherapy, vitamin D

Streszczenie

Wstęp. Naświetlania UVB 311nm (NB-UVB) mają wpływ na ekspresję genów substancji ważnych dla przebiegu łuszczycy poprzez zdolność do naskórkowej produkcji witaminy D.

Cel pracy. Celem pracy była ocena ich wpływu na stężenie 25(OH)D w surowicy w zależności od jego wyjściowej wartości oraz BMI, wieku, płci, nawyków żywieniowych i rekreacyjnych.

Materiał i metody. U 36 chorych mierzono stężenie 25(OH)D w surowicy metodą radioimmunologiczną-RIA przed rozpoczęciem fototerapii (T0), po 1., 3. i 6. tygodniu naświetłań (T1-T3) oraz po 1. i 5. tygodniu od jej zakończenia (T4-T5). Kontrole (28 osób) badano w T0 i T4. Obliczano wartość PASI i BMI, oznaczano fototyp skóry oraz zbierano dane dotyczące stylu życia i danych demograficznych (ankieta).

 Wyniki. Stężenie kalcydiolu w T0 było wyższe u pacjentów 33,21 ng/ml niż w kontroli 25,17 ng/ml (p < 0,05). Tendencja do niższych wartości kalcydiolu u osób starszych, kobiet oraz osób z mniejszym PASI nie była istotna (p > 0,05). Stwierdzono istotną różnicę przyrostu stężenia kalcydiolu pomiędzy oznaczeniem T0 a T4 – wyższą dla grupy o stężeniu < 25 ng/ml. W T4 nastąpił wzrost stężenia kalcydiolu u pacjentów – 50,16 ng/ml (p < 0,05), a spadek w kontroli – 21,37 ng/ml. W T5 stężenie kalcydiolu u pacjentów wyniosło 51,18 ng/ml. Codziennie spożywanie różnych produktów nabiałowych podawało 11-45% badanych. Spozycie ryb deklarowano jako co najmniej raz w miesiącu.


Słowa kluczowe: łuszczyca, fototerapia NB-UVB, witamina D
INTRODUCTION

Psoriasis is a genetic inflammatory dermatosis characterized by abnormally exaggerated epidermal cellular turnover and erythematous lesions with silvery scale (plaque psoriasis). This disease constitutes a significant clinical problem due to its high frequency, chronic and recurrent course and no possibility of an ultimate cure (1, 2).

Due to its efficiency, safety and cost-effectiveness, one of the treatment modalities of moderate psoriasis is narrow-band UVB phototherapy (NB-UVB, with a maximum emission at 311 nm), which appears to influence the disease significant factor’s genes expression by epidermal synthesis of vitamin D (3, 4).

Calcitriol (active metabolite of vitamin D) has been shown to affect leucocytes by phosphorylation of their vitamin D receptor (VDR). Further studies showed that 1α, 25(OH)2D directly influences differentiation of Th2, increasing the production of interleukin IL-4, IL-5, IL-10 and TGF-β, and decreasing the synthesis of IL-2 and INF-γ. In this way calcitriol has an antiproliferative effect on keratinocytes (4). It was also confirmed that calcitriol produced in the skin may have an endo- and autocrine effect within keratinocytes themselves, but also a paracrine effect within the neighbouring cells, mainly by regulating their growth, differentiation and apoptosis, which also explains the efficiency of UVB therapy in psoriasis (5, 6).

Vitamin D is obtained in humans in two ways: by photoconversion of 7-dehydrocholesterol (7-DHC; this is its main source: 90-100%) or can be delivered with food (about 10%), especially fish (i.a. salmon, mackerel, sardines, tuna), milk, train-oil and artificial fortified food (about 10%), especially fish (i.a. salmon, mackerel, sardines, tuna), milk, train-oil and artificial fortified food (7, 8).

Calcidiol constitutes a basic form of vitamin D present in the blood with the biological half-time of 19 days (it can be stored in liver and fat tissue for longer time) (7, 9).

AIM

The aim of this research was to examine whether NB-UVB was able to induce serum 25(OH)D synthesis in relation to its initial level and PASI, BMI, age, sex, dietary and behavioral habits of patients with psoriasis treated with phototherapy.

MATERIAL AND METHODS

The study was performed in 36 adult patients of the Dermatological Clinic of Medical University of Silesia (SUM) in Katowice (7 women and 29 men), aged 21-72 years (47.92 +/- 13.31 (mean +/- SD), BMI 19.03-36.42 kg/m² (27.34 +/- 3.82), skin phototype II and III (Fitzpatrick) who were qualified to NB-UVB phototherapy due to moderate forms of psoriasis (PASI 8.4-14.7 (12.95 +/- 2.74)) and 28 healthy volunteers (13 women and 15 men), aged 26-59 years (43.78 +/- 8.15) and BMI 18.59-32.61 kg/m² (25.61 +/- 11.24). The study obtained the agreement from the SUM Bioethical Commission in Katowice.

The obtained results were subjected to statistical analysis using Statistica™ v.6.0 PL software. Significant differences were defined as p < 0.05.

RESULTS

The mean levels of 25(OH)D in serum (T0) of the patients were 33.21 +/- 16.14 ng/ml (mean +/- SD) and significantly higher in comparison to the control groups (p < 0.05) (fig. 1), and remained within the current recommendations (7). When analysing the group according to the month of the treatment’s beginning, higher levels of calcidiol were found at T0 in group 1 (phototherapy started on the same day. The control group of healthy volunteers for the patients from group I included 23 people, for group II – 17 people, and for group III – 20 people.

25(OH)D serum concentration was measured by radioimmunoassay method (DiaSource 25OH Vitamin D total-RIA-CT Kit) and was checked 6 times: before the first dose of irradiation (T0), after 1st, 3rd and 6th week of irradiation (T1-T3) and in week 1 and 5 after the end of phototherapy (T4-T5). The parameters of controls were measured 2 times (measurement concurrent with measurements T0 and T4 for patients).

The enrolled persons were subjected to a physical examination and biochemical serum tests assessing liver and kidney functions (creatinine, ALT, AST, bilirubine, prothrombin time, INR, fibrinogen in serum) in order to identify possible disturbances influencing vitamin D metabolism. Their dermatological status was assessed using the PASI index according to the Fredriksson’s guidelines, before, during and after the phototherapy. Complete remission was defined as PASI below 3 or its reduction by more than 90% (10, 11).

The body mass index (BMI), Fitzpatrick’s skin type (12) and minimal erythema dose for UVB irradiation (MED, TH-1E lamp (Cosmedico Medizintechnik)) were defined before the treatment started. The data on the disease history in psoriatic patients and the dietary habits, exposition to sun irradiation, demographic information, concomitant diseases, drugs and diet supplements which can influence vitamin D levels in healthy and psoriatic patients were collected in the form of a questionnaire designed by us.

The persons enrolled into the study were informed about its aim and signed written consents for participation. The study obtained the agreement from the SUM Bioethical Commission in Katowice.

The obtained results were subjected to statistical analysis using Statistica™ v.6.0 PL software. Significant differences were defined as p < 0.05.
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respectively – the level defined as hypovitaminosis). The results of mean 25(OH)D concentrations obtained for control group (25.17 +/- 11.59 ng/ml) and for each patient group (28.25 +/- 11.24, 26.2 +/− 13.57 and 20.21 +/− 8.64 ng/ml, respectively) were defined as hypovitaminosis according to the current guidelines. Table 1 shows persons grouped according to the serum 25(OH)D concentration at T0.

Table 1. Serum 25(OH)D level (ng/ml) in patient and control groups at T0.

<table>
<thead>
<tr>
<th>25(OH)D</th>
<th>Recommended level (30-80 ng/ml)</th>
<th>Hypo-vitaminosis (20-30 ng/ml)</th>
<th>Deficiency (10-20 ng/ml)</th>
<th>Deficit (&lt; 10 ng/ml)</th>
<th>High level (&gt; 80 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient groups</td>
<td>18 (50%)</td>
<td>10 (27.78%)</td>
<td>7 (19.44%)</td>
<td>0 (0%)</td>
<td>1 (2.78%)</td>
</tr>
<tr>
<td>Control groups</td>
<td>16 (29.09%)</td>
<td>18 (32.73%)</td>
<td>19 (34.55%)</td>
<td>2 (3.64%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

The significant changes in the level of serum 25(OH)D were observed in periods: T1-T2 (p < 0.001), T2-T3 (p < 0.001), T3-T4 (p < 0.05) and T0-T4 (p = 0.001). The lowest mean calcidiol levels were found at T0, while the highest at T2 (after 3 weeks from the beginning of phototherapy) and were 65.24 +/- 34.63 ng/ml, figure 2. Quantification performed at 5 weeks after the phototherapy ended (T5) showed that the mean 25(OH)D concentrations in the combined patient groups were at the level similar to that of T4 and were 51.18 +/- 21.63 ng/ml.

The psoriatic patients were divided into two groups – with the low (< 25 ng/ml, group I) and high (> 25 ng/ml, group II) initial calcidiol levels and compared between the groups for the increases in the parameter between the phototherapy start (T0) and its end (T4). It was concluded that the increase was the highest in the patients with initially low vitamin D levels in comparison to the patients with the higher values (p < 0.05) (fig. 3).

After the phototherapy ended, the PASI value was significantly lower than before the therapy (p < 0.0001) – it decreased from 12.95 (+/- 2.74) to 1.63 (+/- 1.75) (fig. 4). The percentage of patients with the improvement of their clinical status was 82.35% (PASI 75), and 47.05% (PASI 90).

The lower levels of calcidiol were found (T0) in the sera of patients > 53 yrs (38.69 ng/ml), women (26.56 ng/ml) and in patients with the PASI value of < 12.5 (32.03 ng/ml) in comparison with patients < 53 yrs (28.31 ng/ml), men (34.82 ng/ml) and patients with the PASI value > 12.5 (34.88 ng/ml), although these differences were not statistically significant (p > 0.05). No significant relationships were observed (p > 0.05) between the phototherapy in history and the 25(OH)D concentrations (T0) in the tested patients groups, and between BMI, gender and 25(OH)D concentrations (T0) either in the combined patient groups or in the combined control groups.

No differences between particular patients groups in the serum calcidiol increases (ng/ml) (gender, age, PASI index, phototherapy in history) were found in the successive tests (T0-T4); p > 0.05.

The data on dietary habits were collected on the basis of our own questionnaire – it included questions on frequency of consuming products containing significant amounts of natural or artificially added vitamin D. A positive correlation was detected between the serum 25(OH)D concentrations and the frequency of margarine consumption (p < 0.005) in the patient groups. The mean level of 25(OH)D in the group of 13 persons (36%) consuming margarine every day was increased

Fig. 1. Serum 25(OH)D level (ng/ml) in patient and control groups at T0.

After the end of phototherapy (T4), the mean serum levels of 25(OH)D in the combined tested groups increased to 50.16 +/- 22.29 ng/ml (p = 0.001) and were within the presently valid recommendations. The results obtained for each group were also compliant with the recommended levels and were 64.26 +/- 19.01, 31.99 +/- 15.3 and 49.63 +/- 19.92 ng/ml, respectively. When comparing with T0, a decrease in the percentage of patients with hypovitaminosis and vitamin D deficiency was observed, with an increase in the percentage of patients showing recommended vitamin D levels. The mean calcidiol levels in the control group of 21.37 +/- 14.5 ng/ml indicated hypovitaminosis and the similar results were obtained for group 1 and 3 (28.23 +/- 15.59 and 25.22 +/- 13.48 ng/ml, respectively).

The group 2 showed a decrease in 25(OH)D concentrations down to 10.45 +/- 5.9 (vitamin D deficiency). The increase in the percentage of patients with vitamin D deficiency together with a decrease in the percentage of patients with hypovitaminosis and the recommended 25(OH)D levels were observed. The mean calcidiol concentrations in patient groups at T4 were significantly higher in comparison to control groups (p < 0.05).
The data upon exposition to sunlight and using anti-UV protection were also collected. For the patients groups, the positive correlation between the serum 25(OH)D level and the length of sun exposition around midnoon hours (10 a.m.-4 p.m.) during the weekends was found (p < 0.05). Similar correlations were not present in the control groups. Spending more than 4 hours outdoors was indicated by 75% patients, with only 40% persons in the control groups. The differences in the obtained results can be explained by a more frequent use of creams with UVA/UVB filters by healthy persons (29%) as well as by more systematic application of creams in comparison to psoriatic patients (~17%), although no statistically significant correlations were found between the serum calcidiol levels and using this type of photoprotection (p > 0.05).

No correlations between the serum 25(OH)D levels and the length of exposition to the sun around noon (10 a.m.-4 p.m.) during working days (p > 0.05) were detected – 42% of patients and 80% of controls spent below 2 hours outdoors (including a total lack of exposition declared by 8.3% and 27.3%, respectively), and more than 4 hours outdoors were declared by 17% and 0% participants, respectively. The results are shown in Table 2.

Table 2. Routine sun exposition in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patient groups</th>
<th></th>
<th>Control groups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 h</td>
<td>2-4 h</td>
<td>&gt; 4 h</td>
<td>&lt; 2 h</td>
</tr>
<tr>
<td>Working days</td>
<td>15 (42%)</td>
<td>15 (42%)</td>
<td>6 (17%)</td>
<td>44 (80%)</td>
</tr>
<tr>
<td>Weekends</td>
<td>5 (15%)</td>
<td>4 (11%)</td>
<td>27 (75%)</td>
<td>7 (13%)</td>
</tr>
</tbody>
</table>
No influence of holidays in the countries with high sunlight exposition within preceding 6 months upon serum 25(OH)D levels was found either for the patients or the controls groups (p > 0.05).

DISCUSSION

At the moment, the deficiency of vitamin D is believed to be a common problem worldwide. Technical progress during the last century and changes in the natural environment and lifestyles are potentially responsible for this problem. Some authors also underline the fact of insufficient enrichment of vitamin D in food products present on the market and a commonly mistaken belief that a healthy diet provides sufficient amounts of vitamin D. The most recent studies show how vitamin D deficiency influences the general health status and indicate the need to define standard ranges for different populations and the ways of preventing insufficient supply, such as short exposition to sunlight during midday hours and its supplementation (7, 13-15).

Staberg performed one of the first studies on the influence of phototherapy upon the levels of vitamin D metabolites. Determination of 25(OH)D levels in 10 patients before the start of phototherapy by Goeckerman’s method and after 4 weeks of treatment showed its increase from 24.6 to 54.4 ng/ml (p < 0.001) (16). Osmancevic et al. observed the serum calcidiol increase from 36.8+/−17 to 59.6+/−18.7 ng/ml (p < 0.001) (17), while Ryan’s study showed an increase from 23 to 51 ng/ml, in comparison to the lack of any increase in the control group, in which 75% of tested persons showed its insufficient level (< 20 ng/ml) (18). The study by Lesiak et al., performed in 47 caucasian persons (17 women and 30 men), with the mean age of 43 years, lasting between October and February was aimed at assessing serum 25(OH)D concentrations before the UVB 311 nm phototherapy, and after 10 and 20 sessions. The initial calcidiol level was 26.5 ng/ml, and 16 patients showed the levels < 20 ng/ml. After 10 sessions, an increase up to 38 ng/ml was observed and after the following 10 – up to 43 ng/ml and both measurements were significantly different from the initial levels (p < 0.001). After the end of the treatment, only 4.3% of the patients showed vitamin D deficiency, in comparison to 34% prior to the phototherapy (19).

Our study showed a higher increase of 25(OH)D concentration upon NB-UVB irradiation in the persons with its low initial levels. Similar results were published by Osmancevic et al. (17), Cicarma et al., who tested the influence of NB-UVB upon vitamin D levels in psoriatic and atopic patients (23) and by Bogh et al., who showed a negative correlation between the increase in calcidiol levels upon irradiations and its initial levels (p < 0.001, r² = 0.313). The reason for this phenomenon is unknown, although it may be caused by inhibition of 25-hydroxylase activity in the liver of persons with sufficient serum 25(OH)D levels (24).

In our study, the general frequency of consuming products containing vitamin D among the psoriatic patients was low – everyday milk consumption was declared by 11% patients, 17% declared consumption of other dairy products (such as yogurts, kefirs) and 0% patient ate fish. In healthy persons, the consumption frequency of the above mentioned products was 22%, 45% and 0%, respectively. Despite the fact that healthy persons ate products rich in vitamin D more frequently, consuming was still too low to have any significant influence upon the optimal serum 25(OH)D levels (> 30 ng/ml). The study by Bogh et al. showed a positive correlation between the initial calcidiol levels in serum and consuming fish (p = 0.009; r² = 0.132), with the mean 25(OH)D level higher by 12 nmol/l in the group of persons consuming fish more frequently than once a week (our study showed no fish consumption more often than once a week) (24).

The consumption tables concerning vitamin D content in food products indicate that this vitamin is present mostly in certain fatty fish (including salmon, tuna, mackerel, sardines) or in artificially enriched food...
(including margarine, yogurts, milk, cereals). Milk is the most commonly consumed product from the above, however, the studies suggest that it often does not even contain 80% of the vitamin D levels declared on the label. The vitamin D content in food products is also influenced by the way of food preparation, for example frying fish and by their origin (farmed salmon contains only 25% of vitamin D content found in fish living in their natural environment). Therefore, it has been proposed that the data present in consumption tables are out-of-date and there is a need to work out the new ones (7, 25, 26).

We showed no influence of the length of sunlight exposition during the midday hours (10 a.m-4 p.m.) during working days the calcidiol concentrations. Most persons included in the study (83.3% of patients, 100% of healthy persons) are active workers or students, therefore the declared exposions concerned hours between 2 p.m.-4 p.m., when the UVB dose reaching the earth surface is lower than during the earlier hours. Therefore, such exposition is insufficient to significantly increase the production of vitamin D by the skin. The positive correlation between serum 25(OH)D levels and the length of exposition to the sunlight during the midday hours (10 a.m.-4 p.m.) at weekends in the patient groups (p < 0.05) was not confirmed in the control groups.

The study by Thieden et al. showed a higher correlation of the serum calcidiol levels with the time spent in the sunlight within the day than with the obtained daily UV dose. No influence of creams containing UV filters upon the vitamin D levels was found, which was explained by the fact that they are applied unsystematically and in a too small amount in comparison with the exposed body surface. Therefore, persons who use them can have a longer total exposition to UV than the mean population exposition and the vitamin D is synthesized despite the filters’ use (21).

A tendency to lower calcidiol values (T) in older people, women, persons with smaller intensity of skin changes and in persons with higher BMI value was found in our study, although statistically insignificant. Other studies in psoriatic patients treated with NB-UVB irradiations also showed no significant correlations between the above mentioned parameters i (17, 19, 24, 27).

The literature indicates that the low level of vitamin D in the organism is usually linked with obesity of the central type (visceral) – our study did not enrolled such persons, which may have resulted in the lack of correlation between BMI and 25(OH)D. So far, no disturbances in vitamin D production have been found in the skin of obese people, and its lower circulatory concentration is explained by its significant retention in the subcutaneous adipose tissue and difficulty in its vascular transport. A lack of any relationship between the initial serum 25(OH)D level and the value of the PASI index can be caused by the fact that vitamin D present in the circulation does not penetrate sufficiently into the skin and does not induce there the production of 1.25(OH)2D at a concentration significant for the clinical effect. Therefore, the vital levels of vitamin D in the skin can be obtained only as a result of phototherapy, as observed by Prystowski et al. in 16 psoriatic patients who were divided in placebo and calcitriol receiving groups during a UVB phototherapy. The study showed no significant influence of calcitriol supplementation upon the skin production of vitamin D and an improvement of the clinical status (28).

CONCLUSIONS
On the basis of a statistical analysis of the obtained data, we showed low initial serum vitamin D levels of 25(OH)D (< 30 ng/ml) in most of the study participants, while the overall rate of consumption of products containing vitamin D and everyday exposure to ultraviolet radiation for patients and healthy subjects were too low to have any influence on acquiring its optimal level in the serum. The study confirmed the impact of the initial level of serum 25(OH)D level on the increase in production of vitamin D by 311 nm ultraviolet radiation. The dose of 311nm UVB obtained during the irradiation was sufficient for most patients to obtain a constant, high level of 25(OH)D levels and it masked its seasonal variability observed in the control group. There was a statistically significant increase in the serum levels of calcidiol in patients with psoriasis after phototherapy (p = 0.001), but in some subjects, it still remained lower than recommended. There was no influence of age, gender, PASI index and BMI values and phototherapy used in the past by patients with psoriasis on the serum 25(OH)D levels, and the initial values of the above mentioned parameters did not have any effect on the changes in calcidiol levels in subsequent determinations.

BIBLIOGRAPHY
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